Wegener’s granulomatosis (WG) is an uncommon immunopathologic disease characterized by necrotizing granulomatosis in the upper and lower respiratory tracts, combined with glomerulonephritis. The condition was first described by Klinger in 1933, and then by other investigators including Rossle in 1933, Wegener in 1936 and 1939, and Ringertz in 1947. It is a systemic vasculitis of the small, medium, and occasionally large arterial vessels. Arterioles and venules have also been implicated in the pathogenesis. It is a rare disease with an estimated prevalence of 3 cases per 100,000 people. Whereas the disease is much more common in whites than blacks, it shows no gender affinity; the male to female ratio is 1:1. Although disease onset before adolescence is uncommon—the mean age of onset is approximately 40 years—it can occur at any age.

Clinical Manifestations

In patients with WG, involvement of the upper airways occurs with 95% prevalence. Patients often present with severe upper respiratory tract findings. Paranasal sinus pain and drainage, in addition to purulent or bloody discharge not necessarily associated with nasal mucosal ulceration, may be present. In addition to upper respiratory tract involvement, lower respiratory tract symptoms may be present, including cough, dyspnea, and hemoptysis in 66% of patients. Radiographic findings are varied, but can include alveolar opacities, diffuse hazy opacities, nodules (which may cavitate), and pleural thickening. The second most common clinical manifestation—occurring in 77% of patients—involves the kidneys. Symptoms include acute renal failure with microscopically revealing red cells, red cell casts, and micro- or macroproteinaemia depending on the progression of glomerulonephritis.

Although WG is mainly associated with upper and lower airway and kidney involvement, any area of the body may be affected. For example, involvement of the eyes and skin occurs with relatively high frequency. Eye involvement (52% of patients) ranges from mild conjunctivitis to dacryocystitis, scleral and episcleral inflammation, and (importantly) retro-orbital mass lesions leading to proptosis. Skin lesions can occur as papules, vesicles, palpable purpura, ulcers, or subcutaneous nodules (Table 1).

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### Learning Objectives

- Define Wegener’s granulomatosis.
- Review special problems associated with the administration of anesthetics to patients with Wegener’s granulomatosis.
- Describe systemic changes that occur in these patients.
- Explain the complications of anesthesia in patients using immunosuppressants.
- Apply appropriate preoperative testing and evaluation of patients.
- Discuss findings of laboratory testing of patients.
- Present an anesthetic and analgesic plan for the treatment of patients.
- Delineate risks and benefits associated with the use of regional versus general anesthesia.
- Anticipate, recognize, and manage likely perioperative complications in patients.

### CASE HISTORY

A 33-year-old man presented to the operating room for cystoscopy as part of an evaluation for ureteral obstruction. The patient had previously been diagnosed with Wegener’s granulomatosis, which had been confirmed by renal biopsy 6 years earlier. The patient’s current medications included daily prednisolone and methotrexate. Pulmonary function testing showed a forced expiratory volume in 1 second of 3.69 (81% of predicted) and a forced vital capacity of 4.22 (78% of predicted). Oxygen saturation was measured at 91% on room air. A chest X-ray demonstrated mild hyperinflation with no evidence of infiltrates or granulomatous lesions. Electrocardiography and complete blood count results were within normal limits. A neurologic examination revealed no deficits.

### Preanesthetic Assessment

**Lesson 252: PreAnesthetic Assessment of the Patient With Wegener’s Granulomatosis**

**Written by:**
Paul Rookard, Amir Baluch, BS, Alan D. Kaye, MD, PhD

**Reviewed by:**
Alan D. Kaye, MD, PhD
Professor and Chairman, Department of Anesthesiology, Louisiana State University School of Medicine in New Orleans

**Disclosure Statement:**
Dr. Kaye has disclosed that he is a member of the speakers’ bureau of Baxter.

**Needs Statement:**
Wegener’s granulomatosis, an immunopathologic disease, presents a challenge to the anesthesiologist because of its multisystem involvement: abnormalities of the airway, respiratory, circulatory, renal, and central/peripheral nervous systems are typical. A familiarity with proper perioperative management of these patients is essential. A review of rare disease states has been identified by committee as required knowledge for anesthesiologists.

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At the end of this activity, the participant should be able to:

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9. Cite the incidence and prevalence of Wegener’s granulomatosis.
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The diagnosis is also suggested by the presence of circulating ANCAs that are usually directed against proteinase 3 (c-ANCA). In patients with WG, 25–29 from 65% to >90% are positive for ANCAs. Directed against proteinase 3 (c-ANCA). The former study may reflect a patient population where this pathology may present similarly (manifesting with more severe disease).

Pathogenesis

Histopathologic hallmarks of WG are necrotizing vasculitis of small arteries with granuloma formation that may be either intravascular or extravascular. The complex process begins with an inflammatory event. Later, a highly specific pathogenic immune response follows, and previously unavailable epitopes of neutrophil granule proteins come into play. This mechanism is responsible for generating high serum titers of ANCAs, which are then directed against the primary granules of neutrophils and monocytes. Proteinase-3 and myeloperoxidase (MPO) are the most commonly targeted antigens. The lung involvement generally appears as multiple, bilateral, nodular cavities infiltrates.

Upper airway lesions, usually in the sinuses and nasopharynx, often reveal inflammation, necrosis, and granuloma formation—with or without vasculitis.

The pathogenesis of WG may involve a lack of α-anti-trypsin, which in vivo is the primary inhibitor of proteinase-3. Patients with α-anti-trypsin deficiency are at increased risk for WG, suggesting a role for the increased presence of proteinase-3 at sites of inflammation. Future research may further establish this relationship.

An autoantibody response produces ANCAs directly. Via the process of epitope spreading, the mechanism generalizes to the rest of a macromolecular protein complex. Since the process is antigen-driven, the disease may be intricately linked to T-cell activation—an observation supported by the fact that patients with active WG have much higher levels of CD4+ T-cell and monocytic activation than normal individuals. In addition, extremely high levels of the Thelper type 1 (Th1) cytokines TNF-α and interferon-γ are seen in affected patients. Furthermore, monocyt'es from these patients produce a large amount of interleukin-12, a major inducer of cytokines. Current data suggest that interleukin-10, a mono-ocyte antagonist, may inhibit the Th1 pathway in the disease, as shown in vivo by Ludvigsson and colleagues.44 “Primed” neutrophils have increased cell-surface levels of membrane-associated proteinase-3. When neutrophils are primed, ANCAs can bind, causing abnormal constitutive activation through crosslinking of MPO and proteinase-3, or by the binding of Fc receptors. This pathway is supported by the observation that patients with ANCA-associated vasculitis have increased numbers of primed neutrophils (in renal biopsy specimens) with the level of severity reflecting disease activity. Moreover, the interaction and upregulation of neutrophil activity by endothelial cells may play an important role in pathogenesis.25,29

Recent animal models have provided evidence for the pathogenic potential of ANCAs. Two types of mice have been studied: MPO knockout mice and recombinase-activating gene−2 (RAG-2) deficient mice. The RAG-2 deficient mice lack both T and B cells. In one model, MPO knockout mice were immunized with mouse MPO creating anti-MPO spleno-cytes and anti-MPO antibodies. RAG-2 deficient mice were injected with either anti-MPO splenocytes or control spleno-cytes (those producing no anti-MPO antibodies). Mice that received anti-MPO splenocytes developed clinical features of ANCA-associated vasculitides, whereas RAG-2 deficient mice that received the control splenocytes suffered only a mild immune complex glomerulonephritis. The investigators con-cluded that ANCAs have pathogenic potential and require a functioning immune system to exert this effect.30

Treatment

In patients with WG, aggressive immunotherapy is warranted. Before the advent of glucocorticoid therapy, mortality from the disease was inevitable.2 The mainstay of treat-ment—which has drastically reversed the number of fatalities—is cyclophosphamide combined with oral glucocorticoid. The current recommended dosage is 1.5 to 2 mg/kg per day of cyclophosphamide. Higher dosages of 3 to 4 mg/kg per day may be given for several days to those who are acutely ill with severe disease. The dosing of cyclophosphamide should be adjusted to maintain the leukocyte count above 3,000/mcL, while keeping an absolute neutrophil count above 1,500/mcL. The dosing of corticosteroid for the first month is usually 1 mg/kg per day of oral prednisolone, administered at the beginning of cyclophosphamide therapy. With clinical signs of disease remission during the first month, the dosage may be tapered gradually based on symptoms, ultimately reaching 20 mg of prednisolone (or similar) per day by the end of 2 months.

Complete remission may take from months to 1 to 2 years to achieve. A median time to remission of 12 months was found in 1 study,2 whereas a study in 2003 involving 155 patients with ANCA-associated vasculitides estimated remission rates of 77% within 3 months and 93% by 6 months.31 The former study may reflect a patient popula-tion with more severe disease.

Use of the cyclophosphamide-corticosteroid regimen likely achieves significant improvement in 90% of patients and remission in 75% of patients.32 Unfortunately, as many as half of those whose disease goes into remission suffer a relapse.2 Most relapses are once again induced into remission; howev-er, at some point many patients experience morbidity from the disease such as renal insufficiency, hearing loss, tracheal stenosis, and saddle nose deformity. Some have suggested that monitoring of ANCA titers is useful for indicating signs of active disease, yet such monitoring may be unreliable because titers remain elevated for years after remission.2,35
Because of the toxic side effects of daily cyclophosphamide dosing, monthly intravenous cyclophosphamide must be considered as an alternate regimen. Thus far, studies have shown equal or less efficacy of the drug by monthly dosing compared with oral regimens. If a further treatment option is the administration of a course of methotrexate-prednisolone. This modality has been successful in patients when other regimens have failed. Methotrexate was well tolerated with reversible gastrointestinal disturbances, pneumonitis, and oral ulcers having been reported in some cases. With a methotrexate regimen, there are antagonistic effects on folic acid metabolism; folic acid at 1 to 2 mg per day or folinic acid at 2.5 to 5 mg per week (24 hours after administration of methotrexate) must be incorporated into the regimen. Plasmapheresis, another alternative therapy, may help those with severe pulmonary hemorrhage, antigranulomai basement membrane antibody disease, or dialysis-dependent renal failure.

The medications mentioned above can cause numerous side effects. For example, diabetes mellitus, cataracts, osteoporosis, and the development of cushingoid features are possible adverse effects with glucocorticoid therapy. Cyclophosphamide-related side effects are more severe; at least 30% of patients develop cystitis, 6% develop bladder cancer, 2% develop myelodysplasia, and there is a high risk for permanent infertility in both women and men.

Although the risk is low, pneumonitis caused by pneumonia can be a fatal complication of immunosuppressive therapy in patients with WG occurring in about 6% of patients. Prophyllaxis with trimethoprim-sulfamethoxazole at 160 mg and 800 mg (respectively) 3 times weekly may not only be cost-saving, but also life-prolonging.

After the disease enters remission, maintenance doses with different medications lessen the aforementioned risks for side effects. Methotrexate at a once-a-week initial dosage of 0.3 mg/kg (not to exceed 15 mg) may be administered orally in place of cyclophosphamide. If methotrexate is initially tolerated, the dosage can be increased by 2.5 mg per week, up to 20 to 25 mg per week. Dosing can be maintained for 2 years, then tapered, and ultimately discontinued. An alternative to methotrexate is azathioprine, 2 mg/kg per day. Because there are no head-to-head comparison studies of the 2 drugs, debate is ongoing as to which regimen is superior.

If the patient develops kidney failure, renal transplantation may be performed, although there are limited data regarding long-term outcomes. Case reports indicate that both renal and extrarenal effects can occur. The transplanted kidney, and even the transplanted ureter, may become involved, with possible complications of stenosis and obstructive uropathy. Relapse rates may be lowered as a result of continued immunosuppression, but long-term results in the so-called “cyclosporine era” are unavailable.

Other therapies and maintenance medications such as trimethoprim-sulfamethoxazole, mycophenolate mofetil, and cyclosporine have been used with varying success. Currently, no consensus has been reached on their benefits owing to a paucity of data. Future therapies that use anticytokines, anticytome, anti-T/B-cell antibodies, TIV immunoglobulin, the chemotherapeutic agent etoposide, and the immunosuppressant 15-deoxyspergualin are being studied in the hope of limiting therapeutic agent etoposide, and the immunosuppressant 15-deoxyspergualin are being studied in the hope of limiting its inherent complications.

Depending on the type of surgery that is planned and degree of pathology that is present, a careful anesthetic plan must be developed. As described below, the plan may include awake endoscopy, fiber-optic intubation, or awake tracheostomy if there are significant upper airway lesions. The need for prolonged intubation postoperatively in patients with WG who have significant pulmonary disease should be appreciated. Regional anesthesia techniques can be valzable for certain procedures in patients with limited pulmonary reserve or complex upper airway pathology.

Preoperative Anesthetic Considerations

Preoperative Assessment

The approach to the patient with WG begins with an assessment that includes an evaluation of the upper airway, a chest X-ray, and preoperative evaluation of the upper airway discovers any ulcerating or obstructing lesions, which are present in 95% of cases. Symptoms and complications secondary to such lesions include cough, dyspnea, hemoptysis, pleuritic chest pain, pneumothorax, and pulmonary hemoptysis tolerated, with reversible radiologic findings.

Ventilation-perfusion mismatch of ventilation-perfusion. Bronchial obstruction or destruction can increase pulmonary shunting, and cause arterial desaturation. Frequent suctioning of necrotic debris may be necessary to keep the airways clear. Monitoring of arterial blood gases helps assure that adequate oxygenation and ventilation occur. Even when a regional technique is used, supplemental oxygen is required.

Cardiovascular

Vasculitis of veins, peripheral arteries, and coronary arteries, and granulomas and necrotizing changes are some of the cardiovascular effects of WG. If coronary involvement is present, anesthetic management must avoid situations that may lead to intraoperative myocardial ischemia—such as increased preload or afterload, tachycardia, and coronary artery spasm. In patients with valvular heart defects or cardiomyopathy, hemodynamic status will determine the need for extensive monitoring and use of adjuncts such as pacemakers and vasodilator drugs. Digital arteritis and infarcts at the tips of the digits may decrease the ability to accurately measure oxygen saturation. In these cases, indwelling arterial lines may be used with caution to limit the number of arterial punctures.

Renal

Glomerular destruction and extensive tubular atrophy occur in patients with WG. Caution should be used when administering anesthetics and other drugs that require renal excretion. For example, the following drugs have active or toxic metabolites that are dependent on renal excretion: opioids including morphine and meperidine, diazepam, midazolam, muscle relaxants including vecuronium and pancuronium, and the antihypertensive agent sodium nitroprusside (rarely used today). Rapid accumulation of these metabolites may place the patient in significant danger, possibly leading to prolonged paralysis, low blood pressure, and death. Anesthetic agents that depend predominantly on renal excretion are listed in Table 2.

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be reviewed when applicable. In patients who have been dia-
yzed, particular assessment of fluid balance, electrolytes, and
acid-base status is required. After dialysis, patients may be vol-
able to void after incontinence. The inherent complexity of the dis-
ase may require further study to determine the mechanisms underly-
ing this condition.

References


Use of Succinylcholine

The depolarizing neuromuscular blocking agent, succinyl-
choline, is hydrolyzed by pseudocholinesterase. Conditions
that reduce the activity of this enzyme may prolong the action
of succinylcholine and thus prolong apnea. The cyclophos-
phamide used in the treatment of WG inhibits pseudo-
cholinesterase, possibly in a dose-dependent manner.10,12 While
there are case reports of succinylcholine and even mivacur-
ium causing prolonged apnea,11,12 other researchers have
described uncomplicated and successful usage of succinyl-
choline in patients treated with cyclophosphamide.6,13 Lethal
cardiac complications may result from the administration of
succinylcholine in the presence of hyperkalemia.

Regional Anesthesia

Patients with WG may be candidates for regional anesthe-
 sia, in some of the same concerns for general anesthesia
being applicable to this approach. A WG patient with cardiac
disease may have peripheral neuropathy as part of the clini-
 cal picture.14 Neuropathy may be secondary to underlying
vasculitis of the vasa vasorum of peripheral nerves or in asso-
 ciation with a necrotizing myopathy. A neurologic assessment
should be performed before anesthesia in these cases.15,
16 Complications from bleeding may argue against the use
of a regional technique. A tendency to bleed may develop due
to: thrombocytoppenia as a result of cytotoxic therapy
(cyclophosphamide or methotrexate); low-grade disseminated
infiltrative coagulation caused by circulating immune com-
plexes; or complications from general vasculitis and
granulomatous inflammation with cutaneous, meningeal, or
spinal hemorrhages.17,18 Literature reports have also cited
cases of spontaneous subdural hemorrhage and spinal vas-
cular abnormalities as complications.19,20

The anesthesiologist must weigh the risks and benefits of
regional and general anesthesia. Platelet levels and clotting
studies should be performed. If those findings are normal and
the patient has no neurologic signs, it is likely that a regi-
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dinal approach will produce no complications. Neurologic
deficits, if present, may suggest underlying vascular abnor-
malities or granulomatous infiltration of the cord. In such
cases, computed tomography or magnetic resonance imag-
ing is warranted before attempting neuraxial blockade.6,15

Management of the Case

Risks and benefits were discussed with the patient, who
elected to have a spinal anesthetic. Standard American Soci-
ety of Anesthesiologists monitors were utilized. A 25-gauge
spinal needle with a hyperbaric mixture of 12.5 mg bupiva-
caine in dextrose, 0.2 mg epinephrine, and 15 mcg mepivacaine
was used. The patient tolerated the procedure without inci-
dent. Moderate sedation was administered and there were no
complications.

Conclusion

WG is a complex systemic autoimmune disease that pre-
sents many challenges to the treating clinician. Although
much success has come from currently used cyclophos-
phamide-corticosteroid treatments, vigorous relapse rates
and high morbidity illustrate the need for continued study to
find treatment alternatives. The inherent complexity of the dis-
ease poses specific challenges to the anesthesiologist and
highlights the importance of obtaining an accurate medical
history from the patient. As an ominous disease with systemic
effects, notably on airway and kidney function, careful consid-
eration is required for all aspects of anesthetic care.

Table 2. Perioperative Drugs Predominantly Dependent on Renal Excretion

<table>
<thead>
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